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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09 998,619	11/30/2001	Gregory Conn	3298.1H309US2	5770

31846 7590 01/06/2003

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EXAMINER

LIU, SAMUEL W

ART UNIT	PAPER NUMBER
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1653

DATE MAILED: 01/06/2003

8

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/998,619

Applicant(s)

CONN ET AL.

Examiner

Samuel W Liu

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 04 October 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 1-20 is/are pending in the application.
- 4a) Of the above claim(s) 10-12 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-9 and 13-20 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5
- 4) ☐ Interview Summary (PTO-413) Paper No(s) _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

Applicants' response filed 4 October 2002 as to amendment of claims 3, 9, 13, 15, 19 and 20 has been entered. Note that in the response, applicants appear to amend claim 2; however, there is no actual amendment of the claim; thus, claim 2 is as originally filed. Currently, claims 1-20 are pending. Applicants' affirmation of election of Group I, claims 1-9 and 13-20 with traverse has been acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Therefore, elected claims 1-9 and 13-20 are pending and examined. The following Office Action is applicable to the pending claims 1-9 and 13-20.

The objection(s) and/or rejection(s) not explicitly stated and/or restated below are withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 and 13-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for sulfitolyzing and separating naturally occurring Troponin I (TnI) polypeptide, does not reasonably provide enablement for recombinant (mutant) TnI polypeptide. The specification provides insufficient guidance and no working examples as to how to construct, express, sulfitolyze and chromatograph the mutant polypeptide(s) or peptide(s).

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The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Applicants are in possession of chemically protecting sulfhydryl side chains, deprotecting and chromatographically separating naturally occurring TnI polypeptide. Applicants are not in possession of chemically protecting sulfhydryl side chains and chromatographically purifying all mutant (recombinant) TnI polypeptide.

There would have been numerous mutants, *e.g.*, truncation (deletion), substitution and fusion, which are different and/or distinct from one another in biochemical and physical properties (especially those lack cysteine residue) that would have an impact on chromatographic elution steps which are polypeptide-type-dependent (for instance, different proteins require different elution buffers as well as different elution gradients for an effective elution).

In this regards, the application disclosure and claims have been compared per the factors indicated in the decision *in re* Wands 8 USPQ2d 1400, 1400 (Fed. Cir. 1998). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but not limited to: 1) the nature of the invention; 2) the breath of the claims; 3) the predictability or unpredictability of the art; 4) the amount of direction or guidance presented; 5) the presence or absence of working examples; 6) the quantity of experimentation necessary; 7) the relative skill of those skilled in the art.

Each factor is addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

(1) The scope of the claims/The nature of the invention:

Claims 1-9 and 13-20 of the instant application are directed to a method of sulfitolysis and chromatography of the sulfitolyzed recombinant TnI polypeptide and/or peptide. The claimed recombinant TnI represents a genus encompassing an unpredictable number of mutants, which are substitution, truncation and fusion. The mutants, especially for those containing deletion of cysteine residue(s), have different net charge(s) than intact TnI protein (note that each of *sodium sulfite modified thiol introduces one negative charge into the subject protein*). Chromatographic behavior of such the mutant polypeptides, therefore, would have distinct/different elution profiles, which are unpredictable. Thus, there would have been various elution profiles for various mutant polypeptides during chromatographic separation.

There is insufficient guidance as to the varied chromatographic elution profiles which are governed by different and/or distinct mutant polypeptides sulfitolyzed. The mutated peptide point mutations, would result in obviously distinct elution profiles (see Figures 4 and 5 shown by Paleari, R. *et al.* (1999) *Clinic. Chem.* 45, 21-28). Thus, Chromatographic elution profile(s) for the mutant peptides are unpredictable.

The application is silent in representative description of the genus of TnI mutant proteins isolated by the currently claimed process of ion-exchange chromatography followed by hydrophobic interaction chromatography.

The current application is directed to sulfitolysis of the denatured TnI and recombinant (mutant) TnI polypeptides followed by (a) chromatographic purification of the sulfitolyzed molecules comprising attaching sulphydryl groups to protecting reagent moieties, (b) deprotecting the protected thiol groups in the polypeptides, and (c) refolding of said polypeptides. However, the specification does not provide working examples for steps b) and c),

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especially as to the refolding of recombinant polypeptide molecules. Because the consequence of the refolding, but not descriptive steps thereof, is critical to evaluate the issue concerning bioactive form of TnI protein (including mutant molecules), the application needs to support enablement of the invention. Applicants are not therefore in possession of method of preparing biological active TnI including engineered TnI molecules. The application needs to provide sufficient written description regarding this in order for enablement.

(2) The state of the prior art:

The general knowledge and level of skilled in the art do not supplement the omitted description because specific, not general, guidance is what is needed. The disclosure fails to provide working examples as to how to construct recombinant TnI polypeptide and how to select the recombinant type (*i.e.*, type of mutagenesis, substitution, deletion *etc.*) being subject to chromatography, the skilled artisan is required to perform undue experimentation in order to test, identify and isolate the desired TnI mutant(s) which are protected by sulfitolysis during large scale purification, and then can be reversibly de-sulfitolyzed upon completion of purification.

The current disclosure is directed to using sodium sulfite to carry out sulfitolysis. Yet, sulfite-involved sulfitolysis reaction has a disadvantage regarding uncountable completion of the sulfitolysis by sodium sulfite (see column 2, lines 8-35 of Grossmann, A. US Pat. No. 6342585). The specification provides not guidance or/and working examples regarding this issue.

(3) The quantity of experimentation necessary:

In the absence of working examples with regard to the above mentioned numerous mutant peptides, the unpredictability of the art, the lack of sufficient guidance in the

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specification, and the breadth of the claims, it would take undue trial and error to practice the claimed invention. A skilled artisan would be required to carry out a large body of tests to assess the number of net charges of recombinant polypeptides that are introduced by sulfonylated thiol groups by reacting the polypeptides with sodium sulfite in order for suitable elution during chromatographic separation of the polypeptides.

(4) The unpredictability of the art:

Because (i) there are many recombinant (mutant) TnI polypeptides associated with different length and different number of sulfhydryl groups which are needed to be protected, (ii) as stated above, the completion of sulfite involved sulfitolysis is largely dependent upon mutant structures, and charge distribution in the mutants are not predictable, required is developing necessary elution profiles for purifying the desired TnI recombinant molecules.

In consideration of that incompleteness of sulfite-involved sulfitolysis would leave some disulfides in the sample (note that the current application has changed tetrathionate to sodium sulfite that targets on disulfide linkage), parameter required for and outcome of separation of the oxidized, denatured and sulfonylated TnI mutant polypeptides are unpredictable.

In this regard, therefore, separation of different polyionic chains of the recombinant products on chromatography would require different chromatographic parameters from those set forth for separating non-mutant sulfitolyzed TnI polypeptides in the current application, and would result in different or/and distinct elution profiles. Stubenrauch, K. *et al.* have shown the distinct profiles of interaction of polyionic peptide with ion-exchange matrices (see Figure 1 of *J. Chromatog.* (2000) 737, 77-84). Regardless of truncation, point mutants also produce distinct elution profile (see Figure 4 shown by Paleari, R. *et al.* (1999) *Clinic. Chem.* 45, 21-28).

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Therefore, in the absence of knowledge and information of TnI mutants (recombinant), outcome of separation of the same is highly unpredictable.

(5) The relative skill of those in the art:

The general knowledge and level of skill in the art do not supplement the omitted description with respect to recombinant TnI polypeptides and their degree of completion of the sulfitolysis by sodium sulfite under the same reaction condition for intact TnI. It is noted that the chemical reaction condition set forth in the current disclosure for TnI sulfitolysis cannot be directly applied to mutant TnI polypeptide(s) because some mutants even may not contain cysteine residue(s) (see page 6, lines 7-8 of the current application), which is subject to sulfonylated by sulfite. Therefore, development of chromatographic elution for the mutants would be different from that for naturally occurring TnI peptide (see the rationale in the forgoing statement).

Furthermore, the instant application description is directed to purification of biologically active TnI polypeptide rather than inactive thiol-modified TnI polypeptide(s). However, many TnI mutants would be inactive or partially active absent factual indicia to the contrary. There is insufficient guidance as to which amino acid residue within the polypeptide can be deleted, substituted and whether the resulting TnI polypeptide would maintain the same activity and structure as wild type TnI polypeptide. Honig *et al.* teach that the amino acid residues of a protein that can tolerate structural change (*e.g.*, mutations: conservative substitution or no substitution, addition or deletion) which are critical to maintain the protein's structure will require guidance (see Honig, B. (1999) *J. Mol. Biol.* 293, 283-293). On the other aspect, refolding of the chromatographically separated polypeptides which are in unfold or at least

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partially unfolded state is critical for obtaining fully active TnI (native or mutant). The specification provides no working examples for this, although the specification describes folding process (pages 9-10). The representative working example and guidance are what is needed for enabling the invention.

Given the lack of sufficient guidance and working examples, predicting what amino acid residue(s) or sequence changes can be made to still retain a functional fold is unpredictable and a skilled artisan is not able to supplement the omitted description regarding the mutant design, construction and selection followed by sulfhydryl group protection and chromatography.

In view of the above factors (1-4), the level of skill in this art is high and requires at least a biochemist at Ph.D. level with several years of experience in peptide chemistry, protein purification, molecular biology and biochemistry; yet, even with that level of skill in the art, predictability of the results is still highly variable.

In consideration of each of factors stated above, absent factual data to the contrary, the amount and level of experimentation needed is undue.

The discussions in the response filed 4 October 2002 to the rejection under 35 USC 112, the first paragraph, are fully considered. But they are not persuasive.

The response asserts that the recombinant TnI protein refers to TnI prepared by a biological process TnI (see page 11, the third paragraph). The argument is unpersuasive because the current specification sets forth that (a) the present invention encompasses modified forms of TnI lacking one or two cysteine residues (see page 6, lines 7-8 of the current disclosure; and, this does not eliminate consideration of three (3) cysteines from being missing since missing three

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would have included missing one or more) of *about* 21 KDa; such the recitation refers to that ‘TnI’ is a genus encompassing mutants that are truncated or/and substituted molecules which lacks at least one or two cysteine residue(s); and (b) *natural* TnI is different from *recombinant* TnI since the current application recites “...*natural* TnI **and** properly folded *recombinant* TnI...” (see page 6, lines 17-18); such the recitation discriminates the natural TnI from a recombinant TnI. Thus, the recited “recombinant TnI” in the claims are broadly encompasses mutant form(s) of TnI.

The response asserts that there are guidance and description for recombinant TnI (see the bridging pages 11-12). The assertion is not persuasive. Note that the specification (page 6, lines 19-28) set forth conventional molecular biology methods, while recombinant (mutant) proteins require distinct/different purification procedures, *e.g.*, elution profiles at least; the specification thus does not provide sufficient guidance for this for enablement (see the foregoing statement). Also, please note that applicant’s incorporation of a number of reference publications by reference shown in the specification (page 14) does not have input on rendering purification of mutant TnI enabling. Moreover, lack of guidance and working examples regarding refolding the recombinant TnI polypeptides does not enabling the current invention as well.

The response asserts that the examiner’s contention that the specification is not enabling for chemically protecting sulfhydryl side chain is misplaced (see page 13, lines 7-8). The argument is unpersuasive. Applicants are referred to see the statement at page 4 the second paragraph where states “Applicants are in possession of chemically protecting sulfhydryl side chains, deprotecting and chromatographically separating naturally occurring TnI polypeptide.

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Applicants are not in possession of chemically protecting sulfhydryl side chains and chromatographically purifying all mutant (recombinant) TnI polypeptide".

The response discusses the issue regarding enablement for the refolding of TnI into a bioactive conformation (see page 14, the second paragraph); yet it is noted that "bioactive confirmation" is misspelled; herein, "confirmation" should be "conformation". The current application does not provide the result regarding the refolding. Because the consequence of the refolding, but not descriptive steps thereof, is critical to evaluate the issue concerning bioactive form of TnI protein (including mutant molecules), the application needs to support enablement of the invention.

The response asserts that the examiner adds limitations to applicant's broadest claim (see page 15, lines 1-2). It appears that a "genus"—"TnI" as recited in claim of the current application encompasses the recombinant TnI (mutant TnI) as well as non-engineered TnI proteins. The previous rejection under 35 USC 112, the first paragraph is directed to the mutant TnI protein. There is no limitation has been added to said applicant's broadest claim.

Also, the response asserts that the previous rejection of claim 1 is wrong (see page 14, lines 2-3) which is based on that "the present invention is a method of preparing Troponin I, which method comprises protecting free sulfhydryl group of Troponin I under reducing conditions. The argument is unpersuasive. Note that claim 1 "TnI" encompasses recombinant molecule. Since the current disclosure does not describe structural and functional characteristics of TnI protein in the claims, the recited "TnI" represents a genus encompassing engineered mutants and non-engineered TnI polypeptide molecules. Thus, claim1 is included in the rejection.

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Further, the response asserts that "applicant has provided ample evidence, taken from the specification, to illustrate that the various embodiments of the invention is enable" (see page 15, lines 3-4). The assertion is not true. The current disclosure sets forth that the present invention encompasses modified forms of TnI lacking one or two cysteine residues (see page 6, lines 7-8). However, the specification provide no guidance and/or working examples for the TnI mutants which are truncated form or deletion form that lacks one or two cysteine residues (note that native TnI has only two cysteine residues). Thus, the disclosure does not support enablement of the current invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 1-9 and 13-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and the claims dependent thereto are unclear because the claim fails to indicate steps of the protection to indicate how the protection is accomplished.

Claim 3 is indefinite for lack of antecedent basis for reciting "reacting oxidized recombinant Troponin I" because claims 1 and 2 form which claim 3 depends do not recite "recombinant troponin I". Claim 3 is unclear as to "oxidized"; what are oxidized in Troponin I (TnI) protein? Does said oxidation refer to amino acid oxidation? (note that one of intermediate of amino acid oxidation reaction is deaminated amino acid residue) Therefore, claim 3 needs to

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clarify what is oxidized. Further, claim 3 is ambiguous in the recitation "wherein sulfitolization comprising reacting oxidized recombinant Troponin I (TnI) with sodium sulfite"; the ambiguity is directed to the chemical characteristics of sulfitolization reaction. Sulfitolization recited in claim 2 and claim 3 MUST be an identical process; the object of sulfitolization in claim 2 refers to free sulfhydryl group, while the object of sulfitolization in claim 3 is an oxidized (disulfide-containing) protein that contains no free sulfhydryl groups. Because the type of reactants in a chemical reaction determines characteristics of said reaction, the claim 3 is indefinite in view of the sulfitolization reaction recited in claim 2. See also claim 15.

In addition, please note that the current specification states that "in a *preferred* embodiment, the 'sulfhydryl protecting group' consists of sulfate groups bound through *sulfitolization* with sodium tetrathionate" (see page 8, lines 1-3), and that the current disclosure describes advantage of use tetrathionate (see the bridging pages 7-8). Applicant amends claims 3 and 15 by changing *tetrathionate* to *sodium sulfite* which has not be described in the specification except in "description of figure 1B). Thus, applicant is required to clarify the above paradoxical issue stated above as tosodium sulfite reduction of disulfide linkages *versus* tetrathionate sulfitolization of oxidation of free sulfhydryl groups (see Figure 1 A).

Claim 4 is indefinite for lack of antecedent basis for reciting "the recombinant troponin I".

Claim 6 is indefinite in the recitation "sulfhydryl-protected the recombinant troponin I" (i) for lack of antecedent basis for reciting "the recombinant troponin I" since claim 1 from which claim 6 depends does not set forth preparing "recombinant" TnI protein"; and (ii) because

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of missing a term "group" between "sulfhydryl" and "protected". The dependent claims are also rejected.

Claim 13 recites "the sulfhydryl protected troponin I"; "group(s)" is missing between "sulfhydryl" and "protected", which renders the recitation unclear. The See also claim 6.

Claim 15 recites "reacting oxidized, denatured recombinant Troponin I"; the recitation is unclear as to what is "reacting reduced", and whether or not sulfitolysis comprises sodium sulfite reaction with (a) oxidized sulfhydryl groups or (b) denatured TnI protein wherein sulfhydryl groups are in reduced state.

Response to the rejection under 35 USC 112, the second paragraph

The arguments toward the rejection in the response filed 4 October 2002 are fully considered but they are unpersuasive.

The response discusses the rejection to claim 1 and asserts that claim 1 is definite according to the relevant description in the specification (see the paragraphs at the bridging pages 14-15). In the response, applicants stress that protecting refers to preventing formation of intra- and inter-molecular disulfide bonds of TnI proteins (see page 14, lines 14-16); yet, claim 1 does not clarify this.

The response states that the specification discloses compounds for protecting sulfhydryl groups (see page 14, lines 18-20). Claim 1, however, recites "under reducing condition" but nothing indicates compounds specifically disclosed in the specification. The claim does not clearly indicate what is used for the performing protecting reaction. The claim must have

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sufficient particularity and distinctness by its own; operational characteristics of sulfitolization, although it may be apparent from specification, will not be read into the claim. Thus, applicants' argument is not persuasive.

The response states that applicants have amended claim 3 such that the amended claim is clear (see page 16, the first paragraph). The applicants' amendment of claim 3 by changing 'reduced' to 'oxidized' and 'tetrathionate' to 'sulfite' does not clarify the previously existing indefiniteness of the claim.

As analyzed above, the citation of the *solomon v. Kimberly-Clark corp.* and *Personalized Media communications, LLC v. Int'l Trade Comm'n* at response page 15 is unpersuasive for the reasons indicated above.

Claim Rejections - 35 USC §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined

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was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1, 4-8, 13 and 17-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Al-Hillawi, E. *et al.* (*Eur. J. Biochem.* (1994) 225, 1195-1201).

Al-Hillawi *et al.* teach preparing TnI protein by chromatography under reducing condition (see Figures 2-3, the elution buffer contains reducing reagent dithiothreitol), as applied to present claim 1, 13, 17 and 18. Al-Hillawi *et al.* teach expression of TnI protein which contains silent mutations in the polynucleotide encoding TnI in an *E.coli* strain BL21(DE3) (see "Materials and Methods" section), as applied to claims 4 and 5 of the current application. Here, claim 6 is anticipated because the reference teaches using dithiothreitol (a well known sulfhydryl protecting agent), see reference page 1196, the right column.

Because Al-Hillawi *et al.* also disclose preparation of human TnI by affinity chromatography under non-reducing condition (see page 1198, the first paragraph on the left column), claims 7-8, 13 and 17-18 are anticipated by the Al-Hillawi *et al.* reference as well.

Claims 1, 6 and 8 are rejected under 35 U.S.C. 102(e) as being anticipated by Buechler, K. F. *et al.* (US Pat. No. 6156521).

Buechler *et al.* teach that during the purification of troponin I from tissues, the troponin I is kept in a reduced form, *i.e.*, (free sulfhydryl form) in the presence of reducing reagents (mercaptoethanol and dithiothreitol *etc.*) to prevent intermolecular disulfide formation

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(see col. 9, lines 47-55). Thus, the Buechler *et al.* reference anticipates claims 1, 6 and 8 of the current application.

Claim Rejections - 35 USC §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-9 are rejected under 35 U.S.C. 103(a) as being obvious over Fujita-Becker, S. *et al.* (*J. Biochem.* (1993) 114, 438-444) taken with Lile, J. *et al.* (US Pat. No. 5606031), Chance, R. E. *et al.* (US Pat. No. 4421685), and Buechler, K. F. *et al.* (US Pat. No. 6156521). Note that this a new ground of rejection mainly towards applicants' amendment regarding "sodium sulfite".

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Fujita-Becker *et al.* teach purification of *E.coli.* expressed Troponin I, as applied to claims 1, 4-5 and 17-18 of the current application. Fujita-Becker *et al.* teach the purification using Q-Sepharose column (anion-exchange column) and Phenyl-Sepharose column (a hydrophobic interaction chromatography) (see patent claim 19-20 limitation of "anion exchange column" and "hydrophobic interaction chromatographic support", respectively), as applied to claims 16 and 19-20 of the current application.

Fujita-Becker *et al.*, however, do not teach sulfitolysis of thiol group, denaturing and refolding protein interested.

Lile, J. *et al.* teach a method of the production of biologically active protein comprising i) expressing the protein in *E.coli* (see example 1, column 10), ii) denaturing the expressed protein (see example 2), iii) solubilizing and sulfitolyzing the protein by sulfite salt (see the bridging column 4-5), iv) purifying the sulfonylated protein by chromatography (see claims 1, and 11-12), and v) refolding the purified protein (see example 2, step (a) to (f), columns 12-14), as applied to claims 1 -5, 9, 13-15 and 17-19 of the current application.

Yet, Lile, J. *et al.* do teach explicitly teach deprotecting sulfitolyzed thiol group and purifying TnI protein thereof.

Chance *at al.* teach deprotecting sodium sulfite reacted thiol groups of a polypeptide in order to obtain an active form of polypeptide; the deportation is carried out under reducing condition, *i.e.*, in the presence of dithiothreitol (see column 3, lines 65-69, examples 2 and 4-7, and claim 1, as applied to claim 9 of the instant application.

Buechler *et al.* teach a stabilization of troponin I protein forming a disulfide linkage, *i.e.*, *via* intramolecular oxidation under non-reducing condition (see column 5, lines 4-7) and discuss

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the relation between the oxidation state of the two thiol groups of TnI and purification thereof (see column 9), suggesting that purifying an active form of TnI may be carried out under non-reducing condition, as applied to the application claim 16.

It would have been obvious to one of ordinary skill in the art at the time the invention was made would have combined the teachings of Fujita-Becker, S. *et al.* and Lile, J. *et al.*, (1) because the Lile *et al.* teaching offers an obvious advantages of allowing bacterial produced mammalian protein, which often result in biologically inactive proteins forming inclusion bodies (see column 3, lines 28-44), to be readily and efficiently soluble; Lile's methods involves using sulfitolization for achieving said solubility followed by chromatographic purification, and refolding the purified protein, and (2) because Fujita-Becker *et al.* explicitly teach e method of purifying TnI protein from expression bacterial strain; yet, the reference also describes that purifying troponin protein from the insoluble (*i.e.*, inclusion body) is much more easier than from soluble fraction (see page 441). Because of the above reasons, it would have been obvious to the skilled artisan to combine the above reference teachings to arrive at the disclosed invention.

In addition, since the prior art teaches that cysteine residues of TnI tend to be rapidly oxidized to for intermolecular disulfides (see Buechler *et al.* patent at column 9, lines 47-65), the skilled artisan would have considered protecting thiol groups of TnI during purification and deprotecting the modified thiol groups by removing sulfitolyzing reagent moieties from protected thiol groups followed by the protein refolding as taught by Chance *et al.*

Further, when combined, there would have been the following additional advantages: (i) increase of solubility of *E.coli* expressed mammalian protein and improvement of recovery of

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biologically active protein thereof as taught by Lile *et al.* (see columns 3-4), and (ii) the method developed for purifying TnI protein is suitable for growing crystal for X-ray analysis as taught by Fujita-Becker *et al.*

Given the above motivation one of ordinary skill in the art would have combined the teachings of the above references to develop a method for efficiently isolating biological active TnI protein expressed from bacteria in a large scale. Therefore, the claimed invention was *prima facie* obvious to make and use the invention at the time it was made.

The response filed 4 October 2002 asserts that the previous rejection provides no motivation or teaching to combine the references cited and that the rejection is improper (see the first paragraph at page 20, the last two sentences of the first paragraph at page 21, and the last paragraph at page 21). The argument is not persuasive. The previous rejection under 35 USC 103(a) do provide the teachings, *e.g.*, the Grushoff *et al.* teaching has shown use of tetrathionate to block the sulfhydryl groups of protein in order to facilitate chromatographic purification of a bacterially expressed protein, both the Fujita-Becker *et al.* and the Reiffert *et al.* teachings have demonstrated purification of non-recombinant and recombinant TnI proteins by anion-exchange and hydrophobic interaction chromatography from *E.coli* expression system, and the Hung *et al.* teaching regarding deprotection of S-sulfonated recombinant protein (especially cites "see columns 11-12) in order to obtain refolded TnI protein (*e.g.*, sulfhydryl groups are restored to the their native state) that has biological function in comparison to intact TnI. The rejection also provides the motivation by setting forth the advantages of combining the references' teachings shown on page 12.

The comments at page 16-21 cite several decisions, each appearing to turn on the issue of motivation and hindsight. Given the teachings in the art and reasons indicated here and in the stated ground of rejection these comments in the response are unpersuasive.

Claim Rejection, 35 U.S.C. 101, Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process... may obtain a patent therefore..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-9 and 13-20 are provisionally rejected under the judicially created doctrine of double patenting as being directed to the same invention as that set forth in claims 1-20 of copending Application No. 09903398. Each claim in this application is identical to the claims in the copending application. This is a provisional double patenting rejection because the claims have not in fact been patented. It is of note that the pending claims 3 and 15 of the reference application have been amended filed 29 May 2002 wherein "reduced" and tetrathionate" are changed to:"oxidized" and "sulfite", respectively. Thus, the amended claims 3 and 15 of the

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current application (filed 4 October 2002) are word for word identical to the reference application claims 3 and 15.

In the response file 4 October 2002, Applicant requests to reconsideration of the previous Double Patenting rejection under 35 U.S.C. 101. Since, up to date, Applicant has not abandoned Application 09903398, the rejection stands.

Claims 1-2 and 4-8 are provisionally rejected under the judicially created doctrine of double patenting as being directed to the same invention as that set forth in claims 1-2 and 4-8 of copending Application No. 10287116. Each claim in this application is word to word identical to the claims in the copending application. This is a provisional double patenting rejection because the claims have not in fact been patented.

Claims 1-2 and 4-9 are provisionally rejected under the judicially created doctrine of double patenting as being directed to the same invention as that set forth in claims 1-2 and 4-9 of copending Application No. 10255244. Each claim in this application is word to word identical to the claims in the copending application. This is a provisional double patenting rejection because the claims have not in fact been patented.

Claim Rejections - Provisional Rejection, Obviousness Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible

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harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130 (b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-9 and 13-20 of the instant application are provisionally rejected under the judicially created doctrine of double patenting over claims 1-9 and 13-20 of copending Application No.10287188. This is a provisional double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-2, 4-8, 14 and 16-18 of reference application are word for word identical to claims 1-2, 4-8, 14 and 16-18 of the current application.

Claims 3 and 15 of Application No. 10287188 are variations of claims 3 and 15 of the instant application in that the both claimed methods are directed to use sulfhydryl group protecting reagent, *i.e.*, sodium sulfite (Na_2SO_3) for the current application or sodium tetrathionate ($\text{Na}_2\text{S}_4\text{O}_6$) for Application 10287188.

Claims 9 and 13 of the reference application disclose the same subject matter of Claims 9 and 13 of the instant application; they are obvious variations over each other. Therefore, the

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claims of the present application are not patentably distinct from the claims of Application No. 10287188.

Claims 19-20 of both the reference application and the present application set forth the same limitations for claim 13 from which the claims depend with respect to purifying TnI that contains protected thiol groups using anion exchange and hydrophobic interaction chromatography.

Therefore, the claims of the present application are not patentably distinct from the claims of Application No. 10287188.

Claims 1-9 and 13-20 of the instant application are also provisionally rejected under the judicially created doctrine of double patenting over claims 1-9 and 13-20 of copending Application No. 10255244. This is a provisional double patenting rejection because the conflicting claims have not in fact been patented.

Claim 1-9 and 14-20 of Application No. 10255244 are word for word identical to claim 1-9 and 14-20 of Application No. 10287188. Because the 1-9 and 13-20 of the current application are obvious variations over Application No. 10287188 (see the above statement) and because claim 9 of Application 10255244 is word for word identical to claim 9 of the current application, Claim 1-9 and 14-20 of the instant application conflicts with claims 1-9 and 13-20 of Application No. 10255244, *i.e.*, the instant application and copending application (10255244) claims are obvious variation.

Conclusion

No claims are allowed.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is (703) 306-3483.

The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 703 308-2923. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.



Samuel Wei Liu

December 19, 2002



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